

a single protease inhibitor for initial therapy of antiretroviral naïve individuals [144-147].

In children, available pharmacokinetic data indicate that administration of saquinavir SGC does not result consistently in efficacious plasma levels, possibly due to increased systemic clearance and reduced oral bioavailability. Therefore, saquinavir should not be used as a sole protease inhibitor in combination therapy in children. To achieve adequate drug levels in children, saquinavir-SGC must be administered with a second protease inhibitor that inhibits saquinavir metabolism (e.g., ritonavir or nelfinavir); however, there are only limited pediatric data on appropriate dosing for such combinations [148]. Similarly, saquinavir HGC requires a second protease inhibitor boost to achieve adequate drug levels in children, but no data on appropriate pediatric dosage are available.

Studies of saquinavir in combination with ritonavir or nelfinavir and studies of other dual protease inhibitor combinations are ongoing in treatment-experienced children, but complete data are not yet available [124, 149, 150]. Because information on the pharmacokinetics, safety, and efficacy of dual protease inhibitor combinations in children are limited, with the exception of the co-formulated lopinavir/ritonavir, there are Insufficient Data to Recommend use of dual protease inhibitors as a component of initial therapy in children, although such combinations may have utility as a component of secondary treatment regimens for children who have failed initial therapy.

Fusion Inhibitors

A new class of antiretroviral agents called fusion inhibitors have been identified that inhibit viral binding or fusion to host target cells; the available drugs in this class must be administered subcutaneously. Single and chronic-dosing phase I/II studies of the fusion inhibitor enfuvirtide (T-20) in combination with other antiretroviral drugs in treatment-experienced children have been completed, and have demonstrated that the drug is safe and has an additive anti-viral effect [151]. Enfuvirtide was approved in March 2003 for HIV-infected adults and children 6 years or older for use in combination with other antiretroviral drugs for the treatment of HIV infection in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. There are currently Insufficient Data to Recommend use of enfuvirtide for

initial therapy of HIV infection in children, although the drug may have utility in the treatment of children failing alternative antiretroviral regimens.

RECOMMENDATIONS ON ANTIRETROVIRAL REGIMENS FOR INITIAL THERAPY (Table 11)

There are few randomized, phase III clinical trials of HAART among pediatric patients that provide direct comparison of different treatment regimens; most pediatric drug data come from phase I/II safety and pharmacokinetic trials and non-randomized, open-label studies. Recommendations on the optimal initial therapy for children are continually being modified as new data become available, new therapies or drug formulations are developed, and late toxicities become recognized. Criteria used by the Working Group for recommending specific drugs or regimens include:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- Incidence and types of drug toxicity with the regimen;
- Availability and palatability of formulations appropriate for pediatric use;
- Dosing frequency, and food and fluid requirements; and
- Potential for drug interactions.

The most extensive clinical trial data on initial therapy regimens in adults and children are available for three types of regimens based on drug class: protease inhibitor-based (2 NRTIs plus a protease inhibitor); NNRTI-based (2 NRTIs plus an NNRTI); and NRTI-based (3 NRTI drugs). Each class-based regimen has advantages and disadvantages. Protease inhibitor-based regimens, while highly potent, have a high pill burden and palatability challenges in children (Table 10). NNRTI-based regimens are palatable and effective, but a low genetic barrier to resistance leads to rapid development of drug resistance mutations when therapy does not fully suppress viral replication, and there is cross-resistance among members of this drug class (Table 9). Triple NRTI-based regimens, while sparing of other drug classes, may have lower potency than other regimens (Table 8). As discussed earlier, within each drug class, some drugs may be preferred over other drugs for treatment of children, based on: the extent of pediatric experience; drug formulation,